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(54) Title: *N*-SUBSTITUTED DITHIOCARBAMATES FOR THE TREATMENT OF BIOLOGICAL DISORDERS

(57) Abstract: Methods and compositions for the treatment of proliferative cell diseases, such as cancer, are provided, using N-substituted dithiocarbamates.

United States. CNN Cancer Facts, http://www.cnn.com/HEALTH/9511/conquer_cancer/facts/index.html, page 2 of 2, July 18, 1999.

Although a variety of approaches to cancer therapy (*e.g.*, surgical resection, radiation therapy, and chemotherapy) are available and have been used for many years, cancer remains one of the leading causes of death in the world. This is due in part to the fact that the therapies themselves cause significant toxic side-effects and re-emergence is common.

Antineoplastic agents have been described extensively in a number of texts, including Martindale, *The Extra Pharmacopoeia*, 31st Edition, Royal Pharmaceutical Society (1996).

Antineoplastic agents include:

(i) antifolates;

(ii) antimetabolites (including purine antimetabolites, cytarabine, fudarabine, floxuridine, 6-mercaptopurine, methotrexate, 5-fluoropyrimidine, including 5-fluorouracil, cytidine analogues such as β-L-1,3-dioxolanyl cytidine and 6-thioguanine);

(iii) hydroxyurea;

(iv) mitotic inhibitors (including CPT-11, Etoposide(VP-21)), taxol, and vincristine,

(v) alkylating agents (including but not limited to busulfan, chlorambucil, cyclophosphamide, ifofamide, mechlorethamine, melphalan, and thiotepa);

(vi) nonclassical alkylating agents, platinum containing compounds, bleomycin, anti-tumor antibiotics, anthracycline, anthracenedione, topoisomerase 11 inhibitors, hormonal agents (including but not limited to corticosteroids (dexamethasone, prednisone, and methylprednisone); and

(v) androgens such as fluoxymesterone and methyltestosterone, estrogens such as diethylstilbesterol, antiestrogens such as tamoxifen, LHRH analogues such as leuprolide, antiandrogens such as flutamide, aminoglutethimide, megestrol acetate, and medroxyprogesterone), asparaginase, carmustine, lomustine, hexamethyl-melamine, dacarbazine, mitotane, streptozocin, cisplatin, carboplatin, levamasole, and leucovorin.

For about four decades, the antimetabolite 5-fluorouracil (5-FU), and nucleosides which include this base (*e.g.*, 5-fluoro-2'-deoxyuridine or FdUrd), have remained among the few "standard" drugs effective against solid tumors in man. 5-Fluorouracil is used mainly for the treatment of colorectal, ovarian, renal, breast and head and neck cancers. 5-Fluoro-2'-deoxyuridine is used for the treatment of solid tumors, including hepatic metastases of advanced gastrointestinal adenocarcinomas, renal cell carcinomas, advanced ovarian cancer, and squamous cell carcinomas of the head and neck. The clinical utility of the fluoropyrimidines is limited by the host-toxicity induced by the administration of these compounds. Manifestations of the host-toxicity of the fluoropyrimidines include mainly gastrointestinal epithelial ulceration, myelosuppression and, to a lesser extent, cardiotoxicities, hepatotoxicities and neurotoxicities. A population of cancer patients is intolerant to treatment with 5-fluorouracil and 5-fluoro-2'-deoxyuridine. Moreover, it has also been shown that cancers, treated with fluoropyrimidines, become resistant, *i.e.*, develop tolerance towards these drugs.

Colorectal cancer (CRC) is a multi-step process resulting from the accumulation of mutations in clonal populations of colonocytes. Mutations of the p53 tumor suppressor gene are a relatively late, yet common event in the pathogenesis of colorectal cancer, occurring in over 80% of late adenomas and carcinomas (Fearon, *et al.*, FASEB J. 6, 2789 (1992); Srivastarva, *et al.*, Contemp. Oncol. April 63 (192); Kline, *et al.*, Cancer (Phila. 73, 28 (1994). Conventional therapy for advanced disease, such as cytotoxic chemotherapy and gamma-irradiation, induce DNA damage in proliferating cells. This damage, through undefined mechanism(s), signals the induction of p53, which, in turn, leads to inhibition of cellular proliferation by induction of G_1 cell cycle arrest and, in some instances, apoptosis. Thus, tumors lacking functional p53 are frequently refractory to such therapies (S.C. Righetti *et al., Cancer Res.* 56, 689 (1996); J. S. Kovack *et al., Proc. Natl. Acad, Sci.* U.S.A. 93, 1093 (1996)), emphasizing the importance of developing treatments for advanced colorectal cancer that do not rely on functional p53.

The most effective single chemotherapeutic agent for advanced colorectal cancer to date remains 5-FU. The active metabolite of 5-FU, 5-fluorodeoxyuridine-5'-monophosphate (FdUMP), forms a complex with thymidylate synthase (TS) in the presence of reduced folate, thereby inhibiting enzyme activity, and depleting precursors for DNA synthesis. 5-FU is also incorporated into RNA, altering its processing and function, although how this correlates with cytotoxicity is unknown. Previous data suggest that 5-FU can utilize both p53-dependent and independent pathways (F hard, *et al.*, Pharmacol. Ther. 72, 149

develop the disease. Yang, X.D. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 90, 10494-10498 (1993); Burkly, L.C. *et al.*, *Diabetes* 43, 523-534 (1994); Baron, J.L. *et al.*, *J. Clin. Invest.* 93, 1700-1708 (1994). Monoclonal antibodies to VCAM-1 can also have a beneficial effect in animal models of allograft rejection, suggesting that inhibitors of VCAM-1 expression may have utility in preventing transplant rejection. Oroez, C.G. *et al.*, *Immunol. Lett.* 32, 7-12 (1992).

VCAM-1 is expressed by cells both as a membrane bound form and as a soluble form. The soluble form of VCAM-1 has been shown to induce chemotaxis of vascular endothelial cells in vitro and stimulate an angiogenic response in rat cornea. Koch, A.F. *et al.*, *Nature* 376, 517-519 (1995). Inhibitors of the expression of soluble VCAM-1 have potential therapeutic value in treating diseases with a strong angiogenic component, including tumor growth and metastasis. Folkman, J., and Shing, Y., *Biol. Chem.* 10931-10934 (1992).

U. S. Patent Nos. 5,750,351; 5,807,884; 5,811,449; 5,846,959; 5,773,231, and 5,773,209 to Medford, *et al.*, as well as the corresponding WO95/30415 to Emory University indicate that polyunsaturated fatty acids ("PUFAs") and their hydroperoxides ("ox-PUFAs"), which are important components of oxidatively modified low density lipoprotein (LDL), induce the expression of VCAM-1, but not intercellular adhesion molecule-1 (ICAM-1) or E-selectin in human aortic endothelial cells, through a mechanism that is not mediated by cytokines or other noncytokine signals. This is a fundamental discovery of an important and previously unknown biological pathway in VCAM-1 mediated immune responses.

The induction of VCAM-1 by PUFAs and their fatty acid hydroperoxides is suppressed by dithiocarbamate salts, including pyrrolidine dithiocarbamate (PDTC). This indicates that the induction is mediated by an oxidized signal molecule, and that the induction is prevented when the oxidation of the molecule is blocked (*i.e.*, the oxidation does not occur), reversed (*i.e.*, the signal molecule is reduced), or when the redox modified signal is otherwise prevented from interacting with its regulatory target.

Dithiocarbamates

Dithiocarbamates and related compounds have been reviewed extensively by several authors, including G. D. Thorn *et al.* in a book entitled "The Dithiocarbamates and Related Compounds," Elsevier, New York, 1962. Dithiocarbamates are transition metal chelators clinically used for heavy metal intoxication. F lt, R.C., F.W.J. Sunderman, *et al.* (1977),

et al. (disclosing the use of dethyldithiocarbamate, di(hydroxyethyl)dithiocarbamate, and N-methyl, N-dithiocarboxy-D-glucamine to reduce nephrotoxicity of platinum compounds).

U.S. Patent No. 5,187,193 to Borch *et al.* discloses the use of dithiocarbamate salts and acids to treat damaged bone marrow and to stimulate the production of bone marrow cell growth factors. U.S. Patent No. 5,294,430 to Borch *et al.* discloses that dithiocarbamates can reverse the damage to the blood-forming function of the bone marrow (myelosuppression) caused by treatment with non-platinum antineoplastic agents. The general disclosure of both patents indicates that the nitrogen function of the dithiocarbamate can be part of a heterocyclic ring, or it can be substituted by two alkyl moieties or by one alkyl moiety and one hydrogen. Exemplary dithiocarbamates include diethyldithiocarbamate, N-methyl-glucamine dithiocarbamate and pentamethylene dithiocarbamate.

The CAS abstract for Japanese Kokai 55-015457 (CAS Abstract No. 1981:139788) discloses compounds having the formula $RR^1(CH_2)_mNHC(S)SCH_2CHR^2COR^3$, wherein: R and R^1 can be methyl, ethyl, or together can form a phenyl ring; R^2 is H or methyl; and R^3 is a saturated heterocyclic ring bound to the compound through nitrogen. The abstract indicates that these compounds have anti-inflammatory, anti-rheumatic, hypotensive, immunosuppressant, and anticancer activities.

The CAS abstract for Japanese Kokai 51-105016 (CAS Abstract No. 1977:30075) discloses compounds of the general formula (aralkyl)-$NHC(S)SCH_2CH(NH_2)CO_2R$, wherein R is H, alkyl, alkenyl, alkynyl, cycloalkyl, or lowerhaloalkyl. The abstract indicates that these compounds display antibacterial, anticarcinogenic, and herbicidal activity.

The CAS abstract for Japanese Kokai 49-135942 (CAS Abstract No. 1975:156722) discloses symmetric compounds of the general formula $ROOCCH(NH_2)CH_2SC(S)NHCH_2$-phenyl-$CH_2NHC(S)SCH_2CH(NH_2)COOR$, and indicates that these compounds can be used as antimicrobial drugs and anticancer drugs.

The CAS abstract for French patent publication 2596987 (CAS Abstract No. 1988:548872) indicates that compounds of the formula NH2NHCSNHNH2 proved active against leukemia in a murine model, and also displayed antibacterial effects against Escherichia coli, Staphylococcus aureus, and tuberculosis in vitro.

Research into inflammation and cardiovascular disease has also focused on dithiocarbamates. For example, U. S. Patent Nos. 5,380,747; 5,792,787; 5,783,596; 5,750,351; 5,821,260; 5,807,884; 5,811,449 ,846,959; 5,877,203; and 5,773,209 to

U.S. Patent No. 4,202,832 discloses thiocarbamoylthio fatty acids of the formula aryl-alkylene-NHC(S)S-alkylene-X, wherein X is an acid, ester, amide, or cyano, and indicates that the compounds are useful lipid lowering agents.

U.S. Patent No. 5,563,159 to Kusaba *et al.* discloses dithiocarbinimide derivatives of dithiocarbamate esters useful as agaricidal, fungicidal and insecticidal agents.

U.S. Patent No. 5,344,842 to Missbach discloses thiosemicarbazone derivatives that are useful for treating rheumatoid-type diseases.

It is an object of this invention to provide new methods, compositions, and strategies for treating hyperproliferative disorders, including cancer.

Another object of the present invention is to provide methods of improving the efficacy, and/or reducing the toxicity, of antineoplastic agents administered in the treatment of hyperproliferative disorders.

It is another object to provide new methods and compositions to treat VCAM-1 mediated diseases such as cardiovascular disease and inflammatory disorders.

It is another object to provide new methods of using *N*-substituted dithiocarbamate esters in the treatment of biological disorders.

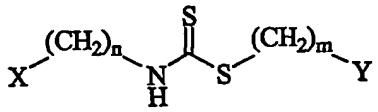
It is still another object to provide new classes of *N*-substituted dithiocarbamate esters, and pharmaceutical formulations from such classes.

SUMMARY OF THE INVENTION

Certain *N*-substituted dithiocarbamate esters have been identified that have activity against hyperproliferative conditions. These compounds can be used to treat hyperproliferative conditions alone, or can be used in combination with one or more other antineoplastic agents. When used in combination with another antineoplastic agent, the combination can inhibit cellular proliferation to a greater extent than either compound administered individually.

Moreover, the combined dosage of antineoplastic agents with these *N*-substituted dithiocarbamate esters exhibits a desired degree of selectivity with respect to transformed (for example cancerous) versus non-tranformed cell types, indicating that the compounds are more toxic to transformed cells than normal cells. In other words, the non-transformed cell types are less susceptible to the growth-inhibitory effects of a combined treatment than transformed cell types. These discoveries provide a therapeutic basis for the use of these

Another example of compounds is defined by the following structure (II):



(II)

wherein:

X is a heterocycle or heteroaryl moiety; Y is CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, or C(O)(OR); n is 1, 2, 3, or 4 and m is 1, 2, 3, 4, 5 or 6.

The invention thus provides:

1. Defined *N*-substituted dithiocarbamate esters, and pharmaceutical formulations of such *N*-substituted dithiocarbamate esters;
2. The use of defined *N*-substituted dithiocarbamate esters in the treatment of cellular hyperproliferation;
3. The use of *N*-substituted dithiocarbamate esters in combination with antineoplastic agents in the treatment of cellular hyperproliferation; and
4. The use of *N*-substituted dithiocarbamate esters to potentiate the efficacy of antineoplastic agents.

It has also been discovered that the defined *N*-substituted dithiocarbamate esters inhibit the expression of VCAM-1, and thus can be used to treat disorders mediated by VCAM-1. Inflammatory disorders that are mediated by VCAM-1, and which can be treated using the *N*-substituted dithiocarbamate esters of the present invention, include rheumatoid arthritis, osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, and multiple sclerosis. Cardiovascular disorders that are mediated by VCAM-1, and which can thus be treated using the *N*-substituted dithiocarbamate esters of the present invention, include atherosclerosis, post-angioplasty restenosis, coronary artery diseases, angina, and small artery disease.

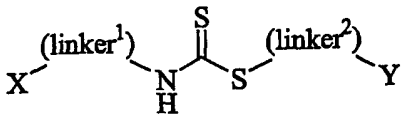
Thus, in still further embodiments the invention provides:

1. Pharmaceutical compositions that comprise a VCAM-1 inhibiting amount of an *N*-substituted dithiocarbamate ester of the present invention, or its pharmaceutically acceptable salt;
2. Methods for treating diseases or disorders mediated by VCAM-1 by administering an effective amount of a *N*-substituted dithiocarbamate ester of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Active Compounds

A preferred class of *N*-substituted dithiocarbamate esters is defined by the following general formula (I):



(I)

wherein:

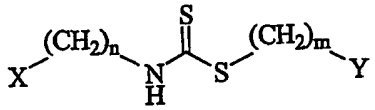
a) X is selected from alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted;

b) Y is selected independently from H, CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, C(O)(OR), amino acid, alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted; and wherein R, R^1 and R^2 are independently H, alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted;

c) linker ^{1} and linker ^{2} are independently alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl, which can be optionally substituted and wherein linker^1 can be a direct bond;

In another embodiment, Y is selected independently from CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, and C(O)(OR).

Another example of compounds is defined by the following structure (II):



(II)

wherein:

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is COOR;

c) n is 1-3; and

d) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is OC(OR);

c) n is 1-3; and

d) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is $C(O)NR^1R^2$;

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-10.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is optionally substituted aryl or heteroaryl;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is $COOCH_3$;

c) n is 0-3; and

d) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted . or heteroaryl;

f) m is 1-12.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted (preferably unsubstituted) 2- or 3-benzofuran, benzothiophene, or indole;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted (preferably unsubstituted) 2- or 3-benzofuran, benzothiophene, or indole;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 1-3; and

e) m is 1-10.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted (preferably unsubstituted) 2- or 3-benzofuran, benzothiophene, or indole;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 1-3; and

d) m is 1-5.

In still another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is an alkyl group;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic,

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, carbohydrate,

c) R^1 and R^2 are independently is H or lower alkyl;

d) n is 0-3; and

e) m is 1-10.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

In another embodiment the invention provides compounds of formula (I) or (II) wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclic-alky;

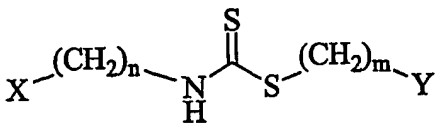
b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

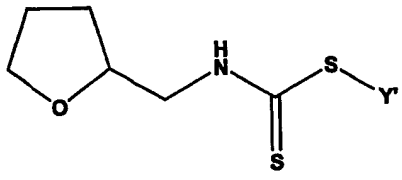
d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-5.



(II)



(III)

Table I

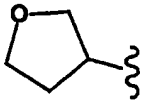
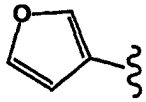
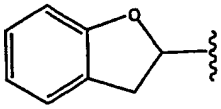
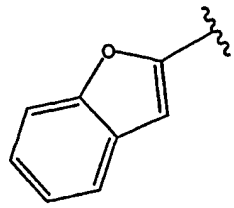
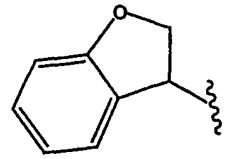
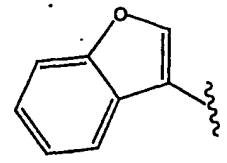
X	Y'	N	m
	$C(O)OCH_3$	1	3
	$C(O)OCH_3$	1	3
	$C(O)OCH_3$	1	3
	$C(O)OCH_3$	1	3
	$C(O)OCH_3$	1	3
	$C(O)OCH_3$	1	3

Table II

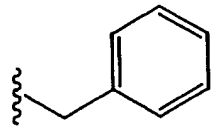
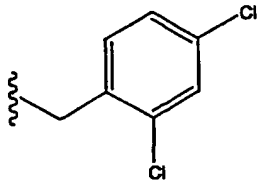
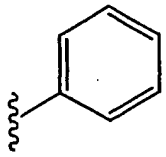
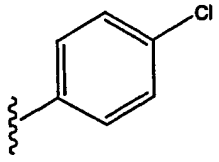
Y'
$CH_2CH(NH_2)C(O)OH$
$(CH_2)_2CH(NH_2)C(O)OH$
$(CH_2)_3C(O)NH_2$
$(CH_2)_3C(O)N(CH_3)_2$





Table I

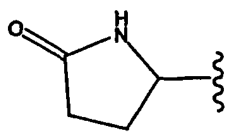
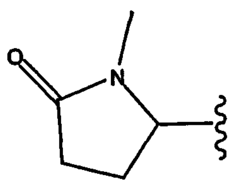
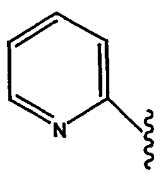
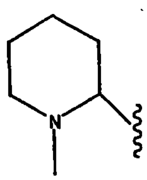
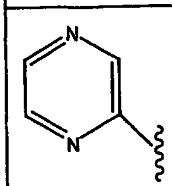
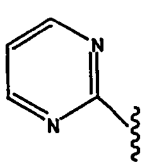
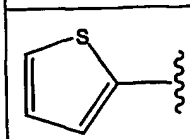
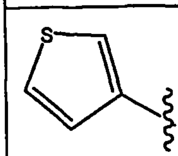
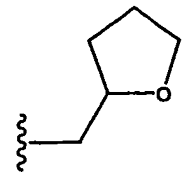
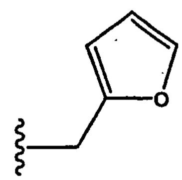
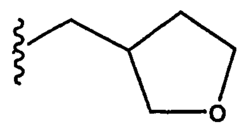
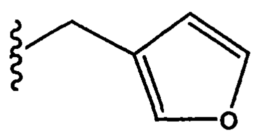
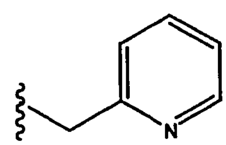
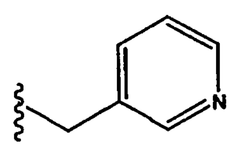
X	Y'	N	m
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3
	C(O)OCH$_3$	1	3

Table II

Y'







(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 4-chloro- phenyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,4- difluoro-phenyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-3- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-3-ylmethyl ester;

4-((S)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

4-((R)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

3-(Furan-2-ylmethylthiocarbamoyl- sulfanyl)propionic acid methyl ester;

3-(Methylthiocarbamoylsulfanyl)propionic acid methyl ester;

3-(Ethoxycarbonylthiocarbamoylsulfanyl) propionic acid methyl ester;

4-(2-Methoxy-ethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrofuran-2-ylmethylsulfanyllthio-carbonylamino)butyric acid ethyl ester;

4-(Cyclohexylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzylthiocarbamoylsulfanyl)butyric acid methyl ester;

Methyldithiocarbamic acid methyl ester;

(5-Chloro-2-methyl-phenyl)dithiocarbamic acid ethyl ester;

4-[2-(1*H*-Indol-2-yl)ethylthiocarbamoyl-sulfanyl]butyric acid methyl ester;

(2-Amino-3-benzylthiocarbamoylsulfanyl)propionic acid;

(3-Methoxybenzyl)dithiocarbamic acid 3,3-dimethyl-2-oxo-butyl ester;

(Pyridin-3-ylmethyl)dithiocarbamic acid 2,5-dichloro-thiophen-3-ylmethyl ester;

4-(Pyrazin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrimidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrothiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzo[*b*]thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester; and

4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester.

The *N*-substituted dithiocarbamate esters of the present invention preferably display VCAM-1 IC_{50} inhibition concentrations of less than about 25, 15, 10, or 5 μM, or LD_{50} concentrations greater than twice, thrice, five times, or ten times the VCAM-1 IC_{50} concentration.

The *N*-substituted dithiocarbamate esters of the present invention also preferably display ApoB/HepG2 IC_{50} inhibition concentrations of less than about 25, 15, or 10 μM, or ApoB/HepG2 LD_{50} concentrations greater than twice, thrice, five times, or ten times the ApoB/HepG2 IC_{50} inhibition concentration.

In still another embodiment the *N*-substituted dithiocarbamate esters do not exhibit any meaningful antioxidant activity, as measured by the leucomethylene blue assay or the OxyBlot assay (as set forth in more detail in the examples hereto). In a preferred embodiment the *N*-substituted dithiocarbamate esters display antioxidant activity which is less than one fifth or even one tenth of that displayed by PTDC (pyrrolidine dithiocarbamate) when measured by the leucomethylene blue assay.

Pharmaceutically Acceptable Salts

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine

produce assymetry (i.e., chirality) in the product, which may be achieved using chrial catalysts or chiral auxiliaries;

vi) diastereomer separations - a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) first- and second-order asymmetric transformations - a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) kinetic resolutions - this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) enantiospecific synthesis from non-racemic precursors - a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) chiral liquid chromatography - a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase. The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) chiral gas chromatography - a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

The term "alkynyl," as referred to herein, and unless otherwise specified, refers to a C_2 to C_{10} straight or branched hydrocarbon with at least one triple bond. The alkynyl group can be optionally substituted in the same manner as described above for the alkyl group.

The term "$-(CH_2)_n-$" represents a saturated alkylidene radical of straight chain configuration. The term "n" can be any whole integer, including 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. The moiety "$-(CH_2)_n-$" thus represents a bond (*i.e.*, when n=0), methylene, 1,2-ethanediyl or 1,3-propanediyl, etc.

The term aryl, as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The aryl group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, acyl, amino, halo, carboxy, carboxamido, carboalkoxy, alkylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in *Greene, et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

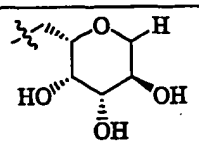
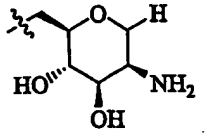
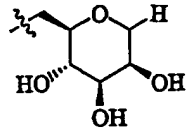
The term heteroaryl or heteroaromatic, as used herein, refers to an aromatic or unsaturated cyclic moiety that includes at least one sulfur, oxygen, nitrogen, or phosphorus in the aromatic ring. Nonlimiting examples are furyl, pyridyl, pyrimidyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, pyrrolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxalinyl, xanthinyl, hypoxanthinyl, and pteridinyl. Functional oxygen and nitrogen groups on the heteroaryl group can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acycl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenelsulfonyl. The heteroaryl or heteroaromatic group can be optionally substituted with one or more moieties selected from the group consisting of hydroxyl, acyl, amino, halo, alkylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in *Greene, et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

magnesium, aluminum, copper, cobalt, nickel, cadmium, sodium, potassium, and the like, or with a cation formed from ammonia, *N,N*-dibenzylethylenediamine, D-glucosamine, tetraethylammonium, or ethylene-diamine; or (c) combinations of (a) and (b); *e.g.*, a zinc tannate salt or the like. Also included in this definition are pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+A^-$, wherein R is as defined above and A is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

The term carbohydrate generally refers to a compound of carbon, hydrogen, and oxygen that contains the saccharose unit or its first reaction product and in which the ratio of hydrogen to oxygen is the same as in water. The carbohydrates of the present invention can, however, be substituted or deoxygenated at one or more positions, in which case the ratio of hydrogen to oxygen will be different than water. Carbohydrates thus include substituted and unsubstituted monosaccharides, disaccharides, oligosaccharides and polysaccharides. The saccharide can be an aldose or ketose, and may comprise 3, 4, 5, 6, or 7 carbons, although pyranose and furanose sugars, and acyclic polyol analogs of the formula $-CH_2-(CHOH)_{3-4}CH_2OH$ are preferred. Preferred carbohydrates are monosaccharides.

Non limiting examples of carbohydrates comprising pyranose and furanose sugars include threose, ribulose, ketose, gentiobiose, aldose, aldotetrose, aldopentose, aldohexose, ketohexose, ketotetrose, ketopentose, erythrose, threose, ribose, deoxyribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, glactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, dextrose, maltose, lactose, sucrose, cellulose, aldose, amylose, palatinose, trehalose, turanose, cellobiose, amylopectin, glucosamine, mannosamine, fucose, phamnose, glucuronate, gluconate, glucono-lactone, muramic acid, abequose, rhamnose, gluconic acid, glucuronic acid and galactosamine.

The carbohydrate can be optionally deoxygenated at any corresponding C-position, and/or substituted with one or more moieties such as hydrogen, halo, haloalkyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester, thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid,

Z	
	
	

Hyperproliferative Disorders

In one aspect the invention provides a method for treating a proliferative cell disease comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof.

In a second embodiment, the *N*-substituted dithiocarbamate ester is administered in combination with another chemotherapeutic agent. As used herein, the term "proliferative cell disease" refers to any cellular disease that is marked by an abnormal rate of cellular mitosis, *i.e.* a rate of cellular mitosis which is greater than the rate of normally dividing cells, and which can be treated with a chemotherapeutic agent. Such cells are referred to herein as "abnormally proliferative cells." A cell proliferative disease may, for example, be associated with increased transcription and translation of an amplified target DNA sequence. The term "proliferative cell disease" denotes malignant as well as non-malignant cell populations that morphologically often appear to differ from the surrounding tissue.

Malignant cell populations can reside in the various organ systems, such as, for example, lung, breast, lymphoid, hematopoietic, gastrointestinal, and genitourinary tract as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer, non-small cell carcinoma of the lung, ovarian cancer, brain cancer, uterine cancer, bladder cancer, cancer of the small intestine, and cancer of the esophagus.

Besides cancer, the term "proliferative cell disease" includes non-malignant and immunological-related cell-proliferative diseases such as psoriasis, pemphigus vulgaris, Behcet's syndrome, acute respiratory distress syndrome (ARDS), ischemic heart disease, post-dialysis syndrome, leukemia, rheumatoid arthritis, acquired immune deficiency syndrome, vasculitis, lipid histiocytosis, septic shock and inflammation in general.

Table V. Examples of neoplastic diseases or malignancies diseases treatable with *N*-substituted dithiocarbamate esters

Organ System	Malignancy/Cancer type
Skin	Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.
Hematological	Acute leukemia, chronic leukemia and myelodysplastic syndromes.
Urogenital	Prostatic, renal and bladder carcinomas, anogenital carcinomas including cervical, ovarian, uterine, vulvar, vaginal, and Those associated with human papilloma virus infection.
Neurological	Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.
Gastrointestinal	Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.
Breast	Breast cancer including estrogen receptor and progesterone Receptor positive or negative subtypes, soft tissue tumors.
Metastasis	Metastases resulting from the neoplasms.
Other	Angiomata, angiogenesis associated with the neoplasms.

Chemotherapeutic Agent

As used herein, a "chemotherapeutic agent" is a type of antiproliferative agent, and particularly is a compound that has biological activity against one or more forms of cancer. Suitable chemotherapeutic agents include antineoplasts. Representative antineoplasts include adjuncts, androgen inhibitors, antibiotic derivatives, antiestrogens, antimetabolites, cytotoxic agents, hormones, immunomodulators, nitrogen mustard derivatives and steroids. Physicians' Desk Reference, 50th Edition, 1996.

Representative adjuncts include levamisole, gallium nitrate, granisetron, sargramostim strontium-89 chloride, filgrastim, pilocarpine, dexrazoxane, and ondansetron. Physicians' Desk Reference, 50th Edition, 1996.

Representative androgen inhibitors include flutamide and leuprolide acetate. Physicians' Desk Reference, 50th Edition, 1996.

Representative antibiotic derivatives include doxorubicin, bleomycin sulfate, daunorubicin, dactinomycin, and idarubicin.

Representative alkylating agents include asaley, AZQ, BCNU, busulfan, bisulphan, carboxyphthalatoplatinum, CBDCA, CCNU, CHIP, chlorambucil, chlorozotocin, *cis*-platinum, clomesone, cyanomorpholinodoxorubicin, cyclodisone, cyclophosphamide, dianhydrogalactitol, fluorodopan, hepsulfam, hycanthone, iphosphamide, melphalan, methyl CCNU, mitomycin C, mitozolamide, nitrogen mustard, PCNU, piperazine, piperazinedione, pipobroman, porfiromycin, spirohydantoin mustard, streptozotocin, teroxirone, tetraplatin, thiotepa, triethylenemelamine, uracil nitrogen mustard, and Yoshi-864. AntiCancer Agents by Mechanism, http://dtp.nci.nih.gov/docs/cancer/searches/standard_mechanism_list.html, April 12, 1999.

Representative antimitotic agents include allocolchicine, Halichondrin B, colchicine, colchicine derivatives, dolastatin 10, maytansine, rhizoxin, paclitaxel derivatives, paclitaxel, thiocolchicine, trityl cysteine, vinblastine sulfate, and vincristine sulfate. AntiCancer Agents by Mechanism, http://dtp.nci.nih.gov/docs/cancer/searches/standard_mechanism_list.html, April 12, 1999.

Representative plant alkaloids include actinomycin D, bleomycin, L-asparaginase, idarubicin, vinblastine sulfate, vincristine sulfate, mitramycin, mitomycin, daunorubicin, VP-16-213, VM-26, navelbine and taxotere. Approved Anti-Cancer Agents, http://ctep.info.nih. gov/handbook/ HandBookText/fda_agent.htm, June 18, 1999.

Representative biologicals include alpha interferon, BCG, G-CSF, GM-CSF, and interleukin-2. Approved Anti-Cancer Agents, http://ctep.info.nih.gov/handbook/ HandBookText/fda_agent.htm, June 18, 1999.

Representative topoisomerase I inhibitors include camptothecin, camptothecin derivatives, and morpholinodoxorubicin. AntiCancer Agents by Mechanism, http://dtp.nci.nih.gov/docs/cancer/searches/standard_mechanism_list.html, April 12, 1999.

Representative topoisomerase II inhibitors include mitoxantron, amonafide, m-AMSA, anthrapyrazole derivatives, pyrazoloacridine, bisantrene HCL, daunorubicin, deoxydoxorubicin, menogaril, N, N-dibenzyl daunomycin, oxanthrazole, rubidazone, VM-26 and VP-16. AntiCancer Agents by Mechanism, http://dtp.nci.nih.gov/docs/cancer/searches/standard_mechanism_ list.html, April 12, 1999.

Representative synthetics include hydroxyurea, procarbazine, o,p'-DDD, dacarbazine, CCNU, BCNU, cis-diamminedichloroplatimun, mitoxantrone, CBDCA, levamisole, hexamethylmelamine, all-trans retinoic acid, gliadel and porfimer sodium.

VCAM-1 Mediated Disease

In another aspect the invention provides a method for treating a disease or disorder mediated by VCAM-1 comprising administering to a patient a VCAM-1 inhibiting effective amount of a *N*-substituted *dithiocarbamate ester* of the present invention, or a pharmaceutically acceptable salt thereof. Exemplary effective amounts and modes of administration are set below in "Pharmaceutical Compositions and Modes of Administration." The compound can be administrered alone or in combination with other active compounds.

Nonlimiting examples of noncardiovascular inflammatory diseases or disorders that are mediated by VCAM-1 and which can be treated by administering the compounds of the present invention include rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and chronic solid organ rejection, and multiple sclerosis. Nonlimiting examples of cardiovascular diseases or disorders that can be treated by mediating VCAM-1 expression and which can be treated by administering the compounds of the present invention include atherosclerosis, post-angioplasty restenosis, coronary artery disease, angina, and small artery disease.

Examples of compounds for treating VCAM-1 mediated conditions include the compounds of formula II wherein:

a) X is an optionally substituted 2- or 3- benzofuran, benzothiophene, or indole;

b) X is an optionally substituted carbohydrate; or

c) X is an optionally substituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl.

EXAMPLES

The following examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way.

Example 1: Effect of *N*-substituted dithiocarbamate esters with and without 5-fluorouracil on the growth of transformed and nontransformed cells

The following example was undertaken to determine the effect of *N*-substituted dithiocarbamate esters with and without 5-fluorouracil on the growth of a variety of transformed and non-transformed cells. Information concerning the cell lines used in this example are given in Table 1.

Dithiocarbamate: The dithiocarbamate tested in this examples is 4-(tetrahydro-furan-2-ylmethylthiocarbamoylsulfanyl)-butyric acid methyl ester, which is referred to below as NDE.

Results/Discussion:

The data in Tables 2 & 3 demonstrate in two colorectal cell lines (SNU-C5 and DLD-1) a dose- and time-dependent inhibition of proliferation when cells are treated with dithiocarbamate. This inhibition is potentiated at the lower doses of dithiocarbamate (NDE) when combined with a low dose of 5-FU. Similar results were obtained with the colorectal cell line DLD-1 (Table 3).

The effect of dithiocarbamate in additional solid tumor cell lines and three non-transformed cell types was determined. As shown in Figure 1 there is a time-dependent inhibition of proliferation in all of the transformed cell lines (HeLa, H1299, MCF-7, Saos-2, and T98G) at 10μM dithiocarbamate in combination with 0.1μM 5-fluorouracil. At this concentration of 5-FU, there was no significant inhibition of proliferation of any cell types when tested alone. In all transformed cell types, by 72 hours the value is significantly different ($p<0.05$) when compared to both control (DMSO) treated-cells and compared to cultures treated with 0.1μM 5-FU alone. In some cell types statistical significance is also observed at the 24 and 48 hour time point.

In the non-transformed cell types HASM and HAEC, a time-dependent inhibition of proliferation was not observed. The NHBE cells appeared more sensitive to inhibition of proliferation and exhibited a time-dependent inhibition of proliferation. However, the level of inhibition was generally less than that observed with the other transformed cell types excluding MCF-7.

Table 2. Anti-proliferative effects of dithiocarbamate (NDE) with and without 5-fluorouracil on proliferation of SNU-C5 colorectal carcinoma cells. Data is represented as percent of control (cells with no drug treatment).

	5-FU Alone (1μM)	NDE	NDE + 5-FU (1μM)
5-FU (1μM)			
24 HOURS	108.9		
48 HOURS	85.5		

	5-FU Alone (1μM)	NDE	NDE + 5-FU (1μM)
72 HOURS		141.90±14.87	82.50±11.91
NDE (100μM)			
24 HOURS		53.77±5.28	51.27±2.63
48 HOURS		39.80±6.27	39.90±4.25
72 HOURS		0.27±0.27	0±0

* Values indicated are percent of control.

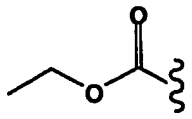
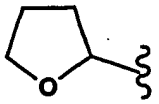
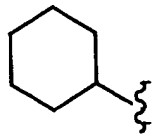
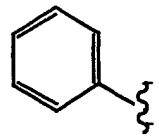
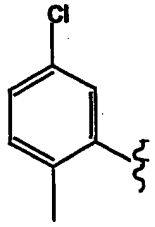
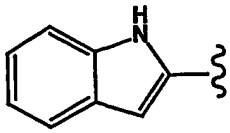
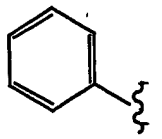
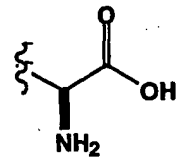
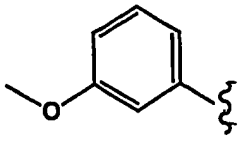
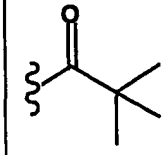
Example 2. Effect of *N*-substituted dithiocarbamate esters on VCAM-1 Inhibition

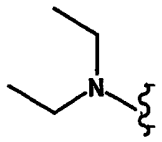
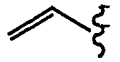
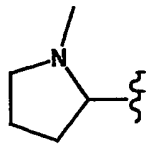
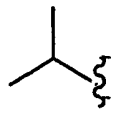
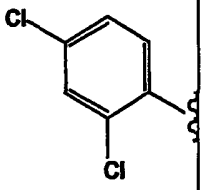
The VCAM-1 assay is an enzyme immunoassay to detect tumor necrosis factor alpha (TNF-α) induced Vascular Adhesion Molecule (VCAM-1) expression in endothelial cells.

Methods:

Cell culture: Human endothelial cells (HAEC) were purchased from Clonetics and maintained in EGM media (Clonetics) supplemented with 5% fetal bovine serum (FBS). In a typical experiment, cells were seeded in 96-well plates. The next day cells were stimulated with TNF-α (1ng/ml) purchased from Boehringer Mannheim in the presence or absence of compounds dissolved in dimethylsulphoxide (DMSO). To establish a dose curve for each compound, four concentrations in 2 fold increments were used. Cells were exposed to TNF-α and compounds for approximately 16 hours. The next day, cells were examined under microscope to score for visual signs of toxicity.

Immunoassay: Media was discarded and the cells were washed once with Hanks buffered saline solution (HBSS)/ phosphate buffered solution (PBS) 91:1). Primary mouse monoclonal antibody against VCAM-1 purchased from Southern Biotechnology Associates (0.25μg/ml in HBSS/ PBS + 5% FBS) was added and incubated at 37°C for 30 minutes. Cells were washed with HBSS/ PBS three times, and secondary antibody horse radish peroxidase (HRP)-conjugated goat anti-mouse IgG purchased from Southern Biotechnology Associates (1:500 in HBSS/ PBS + 5% FBS) was added and incubated at 37°C for 30 minutes. Cells were washed with HBSS/ PBS four times and peroxidase substrate 3.3', 5, 5'-tetramethyl-benzidine (TMB) was added and incubated in the dark at room temperature

X	Y'	N	m	VCAM-1 IC_{50} (μM)	II or III
		3	1	5	II
	$C(O)OCH_3$	1	3	40	II
	$C(O)OCH_3$	1	3	25	II
H	H	1	1	NE	II
	H	0	2	NE	II
	$C(O)OCH_3$	2	3	5	II
		1	1	7	II
		1	1	2	II

X	Y'	N	m	VCAM-1 IC_{50} (μM)	II or III
	$C(O)OCH_3$	2	3	37	II
	$C(O)OCH_3$	1	3	30	II
	$C(O)OCH_3$	2	3	18	II
		1	1	32	II
N/A	CH_3			6.5	III
N/A	$CH_2C(O)OCH_3$			10	III
N/A	$(CH_2)_2C(O)OCH_3$			3	III
N/A	$(CH_2)_3C(O)OCH_3$			1.5	III
N/A	$(CH_2)_5C(O)OCH_2CH_3$			11	III
N/A	$(CH_2)_3C(O)OH$			7	III
N/A	$(CH_2)_3C(O)CH_3$			7	III
N/A	$(CH_2)_3CN$			3	III

Methods:

Cell culture: Normal human bronchial epithelial cells (NHBE) were purchased from Clonetics. They were cultured in BEGM (Clonetics) media without retinoic acid. In a typical experiment, the cells were seeded in 24-well plates. Media was changed to BEGM without retinoic acid (RA) and hydrocortisone (HC) 24 hr before dosing. Cells were then exposed to compounds in fresh BEGM without RA and HC for 20 min at 37°C, subsequently stimulated with TNF (10ng/ml) and IL-4 (20ng/ml) purchased from Boehringer Mannheim for another 20 min at 37°C. All compounds were dissolved in DMSO and the final concentration of DMSO was 0.2%.

Immunoblot: Cells were washed 3 times with cold PBS, and lysed in 100µl/well 1X RIPA buffer (25 mM Tris pH7.6, 150mM NaCl, 2mM EDTA, 1% IGEPAC, 0.5% deoxycholate, 0.1% SDS), 50mM DTT, 1mM PMSF, 10µg/ml leupeptin, 1µl/ml aprotinin. The cell lysates were clarified by centrifugation. 5 µl of the lysates were mixed with 5µl 12% SDS (OxyBlot™ kit) and 10µl of 1X 2,4-Dintirophenylhydrazin (DNPH) (OxyBlot™ kit). As negative controls, a parallel set of lysates was mixed with 12% SDS and a 1X Derivatization-Control Solution (OxyBlot™ kit). All samples were then incubated at room temp for 15 min, followed by adding 15 µl of 12% SDS to each sample.

Samples were fractionated by 4-20% gradient SDS-PAGE (NOVEX), transferred onto nitrocellulose filters (MSI) and incubated with the filters in Blocking/Dilution Buffer (OxyBlot ™ kit) for 1 hour with gentle shaking. Primary antibody (OxyBlot™ kit) was diluted 1:150 in Blocking/Dilution buffer and added to the filters for 1-hour incubation at room temperature. The filters were then washed in 1X PBS-Tween four times. Secondary antibody (OxyBlot™ kit) was diluted 1:300 in Blocking/Dilution Buffer and added to the filters for 1-hour incubation at room temperature. The filters were washed as previous, exposed to chemiluminescence reagents according to the manufacturer's directions and developed by autoradiography film.

Results:

The results from the derivatized samples are shown in Figure 4. The negative control samples did not have any signal on the film.

Example 6. Eotaxin Assay of 4-(tetrahydrofuran-2-ylmethylthiocarbamoylsulfanyl)-butyric acid methyl ester

The eotaxin assay is an enzyme immunoassay to measure tumor necrosis factor alpha (TNF-α) and interleukin-4 (IL-4) induced expression of eotaxin in a human epithelial cell line (BEAS-2B).

Methods:

Cell culture: BEAS-2B cells purchased from ATCC and maintained in DMEM/F12 plus 10% serum and penicillin plus streptomycin. In a typical experiment, cells were seeded in 96-well plates. The next day cells were stimulated with TNF (10ng/ml) + IL-4 (20nm/ml) in the presence or absence of compounds dissolved in dimethylsulphoxide (DMSO) in DMEM/F12 plus 1% rabbit serum albumin (RSA). To establish a dose curve for each compound, three concentrations in 2 fold increments were used. Cells were exposed to cytokines and compounds for approximately 16 hours. The next day, the cells were examined under microscope to score for visual signs of toxicity. The culture media was used to measure eotaxin level.

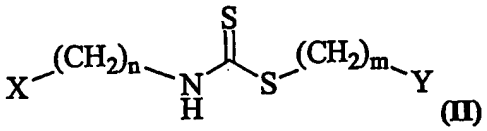
Immunoassay: 100μL of anti-human eotaxin monoclonal antibody (3μg/mL) purchased from R & D Systems was used to coat 96-well plates overnight at room temperature. The next day the plates were washed with 0.05% Tween 20 in 1X PBS three times and blocked by adding 300μl of 1X PBS containing 1% BSA, 5% sucrose and 0.05% NaN_3 to each well for an hour at room temperature. The plates were washed as previously described. 100μL of the culture media (no dilution is required) or eotaxin standard (1000, 500, 250, 125, 62.5, 31.25, 15.62, 0 pg/ml in 0.1% BSA, 0.05% Tween 20 in TBS) were added to each well and incubated at room temperature for 2 hr. The plates were washed as previously described. 100μl of the biotinylated anti-human eotaxin antibody purchased from R & D Systems (150ng/ml, diluted in 0.1% BSA, 0.05% Tween 20 in TBS) was then added and incubated at room temperature for 2 hr. After another wash, 100μl of Avid-HRP (1:2000 in 0.1% BSA, 0.05% Tween 20 in TBS) purchased from Boehringer Mannheim was added and incubated at room temperature for 30 min. After the final wash, 100μl TMB was added. 2N sulphuric acid stopped the color development and data were collected by a microplate reader set at O.D. 450nm. The results were expressed as the percentage of control sample (cells stimulated by TNF without any compound). IC_{50} is the concentration of compound required to inhibit 50% of the TNF + IL-4 stimulated signal.

concentrated by rotary evaporation to give the crude dithiocarbamate ester. Purification is accomplished by re-crystallization from a suitable solvent system or by chromatography to give the desired *N*-substituted dithiocarbamate ester.

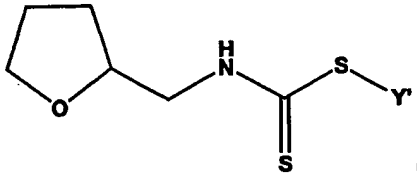
Protocol B (via intermediate isothiocyanate)

A quantity of thiocarbonyldiimidazole (1.02 eq.) is dissolved in chloroform. De-ionized water is added followed by 0.5 eq. of K_2CO_3. A quantity of amine (1.0 eq.) in chloroform is added to the mixture. The resulting mixture is stirred. The progress of the reaction is monitored by thin layer chromatography. The immiscible layers are separated, and the organic layer is concentrated by rotary evaporation to give the crude isothiocyanate. The crude isothiocyanate is dissolved in a solvent (*e.g.* DMF) suitable for the subsequent coupling reaction with a thiol (1 eq.). The progress of the reaction is monitored by thin layer chromatography. A base (*e.g.* NaH) may be added to accelerate the reaction. The reaction is quenched by partitioning between an organic solvent (*e.g.* ethyl acetate) and water. The organic phase is separated and dried over anhydrous Na_2SO_4 or $MgSO_4$. Removal of the drying agent is followed by removal of solvent by rotary evaporation to give the crude dithiocarbamate ester. Purification is accomplished by chromatography or by re-crystallization to give the desired *N*-substituted dithiocarbamate ester.

The compounds in the table below are made according to the synthetic protocols A or B in Example 7.



(II)



(III)

Table 4

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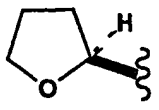
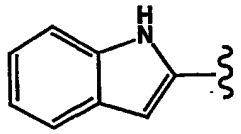
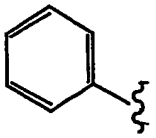
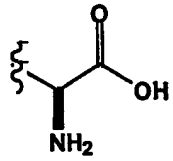
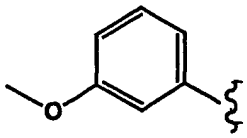
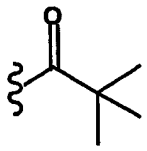
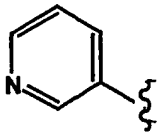
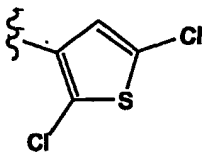
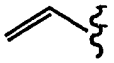
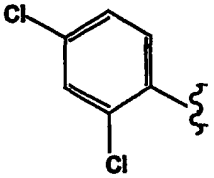
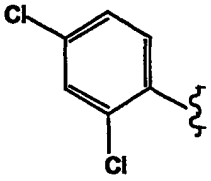
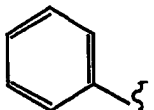
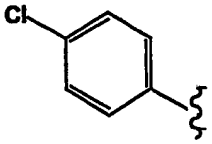
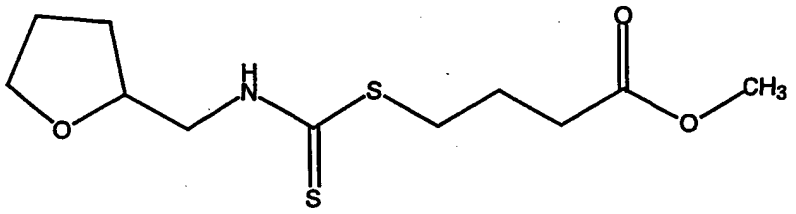
	$C(O)OCH_3$	1	3	3	II

X	Y'	N	m	VCAM-1 IC_{50} (μM)	II or III
	$C(O)OCH_3$	2	3	5	II
		1	1	7	II
		1	1	2	II
		1	1	1.5	II
	$NH_2 \cdot HCl$	1	2	12	II
		1	1	8	II
	H	2	1 2	30	II
CH_3O		3	0	6	II

X	Y'	N	m	VCAM-1 IC_{50} (μM)	II or III
N/A	$(CH_2)_5C(O)OCH_2CH_3$			11	III
N/A	$(CH_2)_3C(O)OH$			7	III
N/A	$(CH_2)_3C(O)CH_3$			7	III
N/A	$(CH_2)_3CN$			3	III

Example 8. 4-(tetrahydrofuran-2-ylmethylthiocarbamoylsulfanyl)-butyric acid methyl ester (NDE)



To a solution of tetrahydofurfurylamine (2 mL) in EtOH (20 mL) were added 5 N NaOH (3.9 mL) and carbon disulfide (1.17 mL), and the mixture was stirred for 1.5 h. Methyl 4-chlorobutyrate (2.4 mL) was then added, and the mixture was stirred overnight. Upon quenching with saturated NaCl solution the mixture was extracted with ether. Chromatography on silica gel gave the desired 4-(tetrahydrofuran-2-ylmethylthiocarbamoylsulfanyl)-butyric acid methyl ester product (1.1 g).

Pharmaceutical Compositions and Modes of Administration

Animals, including mammals and specifically humans, suffering from any of the above-described conditions can be treated by the topical, systemic or transdermal administration of a composition comprising an effective amount of a *N*-substituted dithiocarbamate ester or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier or diluent. When treating proliferative cell diseases, the dithiocarbamate can be coadministered with a chemotherapeutic agent, which may also be

than about 30 mol % cholesterol, the selected proportion being adjusted for the optimal therapy.

A variety of techniques to produce microparticles have been described in the prior art. For example, United Kingdom Patent Application No. 2,234,896 to Bodmer *et al.* describes a method of forming microparticles by mixing a solution of the polymer dissolved in an appropriate solvent with a solution of a drug. Microparticle formation is then induced by the addition of a phase inducing agent. European Patent Application 0 330 180 to Hyon *et al.* describes a process for preparing polylactic acid-type microparticles by adding a solution of a drug and a polymer in a mixed solvent to a phase inducing agent and evaporating the original solvent microparticle formation. Other examples of processes for preparing microparticles by phase separation technique have been described in U.S. Pat. Nos. 4,732,763 to Beck *et al.* and 4,897,268 to Tice *et al.* and by Ruiz *et al.* in the International Journal of Pharmaceutics (1989) 49:69-77 and in Pharmaceutical Research (1990) 9:928-934.

The *N*-substituted dithiocarbamate esters and/or chemotherapeutics agents may be administered orally in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the substance may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of the substance. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of substance in such therapeutically useful compositions is such that an effective dosage level will be obtained.

Tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the

preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

Injectable solutions are particularly advantageous for local administration of the therapeutic composition. In particular, intra-muscular injection can be used to deliver the dithiocarbamate and chemotherapeutic agent directly to a tumorous growth. Intra-articular injection is a preferred alternative in cases of arthritis where the practitioner wishes to treat one or only a few (such as 2-6) joints. Additionally, the therapeutic compounds are injected directly into lesions (intra-lesion administration) in appropriate cases. Intradermal administration is an alternative for dermal lesions.

The therapeutic compound or compounds are optionally administered topically by the use of a transdermal therapeutic system (see, Barry, Dermatological Formulations, (1983) p. 181 and literature cited therein). While such topical delivery systems have been designed largely for transdermal administration of low molecular weight drugs, by definition they are capable of percutaneous delivery. They can be readily adapted to administration of the therapeutic compounds of the invention by appropriate selection of the rate-controlling microporous membrane. Topical application can also be achieved by applying the compound of interest, in a cream, lotion, ointment, or oil based carrier, directly to the skin. Typically, the concentration of therapeutic compound in a cream, lotion, or oil is 1-2%.

For drug targeting to lung tissue, the therapeutic compound is formulated into a solution, suspension, aerosol or particulate dispersion appropriate for application to the pulmonary system. The therapeutic agent may be inhaled via nebulizer, inhalation capsule, inhalation aerosol, nasal solution, intratracheal as a solution via syringe, or endotracheal tube as an aerosol or via as a nebulizer solution. Aersols are prepared using an aqueous aerosol, liposomal preparation or solid particles containing the compound. A nonaqueous (*e.g.* fluorocarbon propellant) suspension could be used. Sonic nebulizers are preferred because they minimize exposing the therapeutic compound to shear, which can result in degradation of the compound.

Sublingual tablets are designed to dissolve very rapidly. Examples of such formulations include ergotamine tartrate, isosorbide dinitrate, isoproterenol HCl. The formulation of these tablets contain, in addition to the drug, a limited number of soluble excipients, usually lactose and powdered sucrose, but occasionally dextrose and mannitol.

most conveniently, 50 to 500 mg of active ingredient per unit dosage form. Ideally, the *N*-substituted dithiocarbamate ester should be administered to achieve peak plasma concentrations of from about 0.5 to about 75 μM, preferably, about 1 to 50 μM, most preferably, about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the substance, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the substance. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the substance.

When the *N*-substituted dithiocarbamate ester is coadministered with a chemotherapeutic agent for the treatment of a cellular proliferative disorder, the dosing will generally be based upon the accepted dosing rate and schedule for the chemotherapeutic agent, and the level of *N*-substituted dithiocarbamate ester which maximally potentiates the efficacy of the chemotherapeutic agent without inducing unacceptable levels of cytotoxicity. However, it should be understood that any concentration of the *N*-substituted dithiocarbamate ester can be administered to potentiate the activity of the chemotherapeutic agent.

The *N*-substituted dithiocarbamate ester and/or chemotherapeutic agent may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day.

Biodegradable Implants

In one embodiment the invention provides a biodegradable implant that is inserted into the void created by surgery for removal of a tumor. By the term "biodegradable" is meant capable of being completely removed from the localized area, by physiological metabolic processes. The implant contains the *N*-substituted dithiocarbamate ester of the present invention and optionally a chemotherapeutic agent, and is present in a sustained release formulation that permits sustained local delivery to the excision site for a substantially predetermined period of time. The implant is useful for any surgery which removes a cancerous tumor from a patient's body, and is particularly useful following the removal of a cancerous growth from the brain, breast, or other bodily tissue.

A number of sustained-release implants are known in the art. Most implants are "matrix" type, and comprise an active compound dispersed in a matrix of a carrier material. The carrier material may be either porous or non-porous, solid or semi-solid, and permeable

Preferable compositions are pharmaceutically acceptable, biodegradable, and meet the particular release profile characteristics that are required to achieve the administration regime involved.

The implant typically comprises a base composition which acts as a matrix to contain and hold the contents of the implant together. The base composition can, in turn, comprise one or more constituents. Examples of base compositions include polymers and copolymers of anhydrides, orthoester, lactic acid, glycolic acid, dioxonane, trimethylene carbonate, ϵ-caprolactone, phosphazene, andglyceryl monostearate.

In one embodiment the base composition for the matrix comprises a polyanydride, which can be synthesized via the dehydration of diacid molecules by melt condensation. Degradation times can be adjusted from days to years according to the hydrophobicity of the monomer selected. The materials degrade primarily by surface erosion and possess excellent in vivo compatibility. In one embodiment the polyanhydride is formed from sebasic acid and hexadecandioic acid (poly(SA-HDA anhydride). Wafer-like implants using this base composition have been approved for use in brain cancer, as Giadel®, by Guilford Pharmaceuticals.

The implant optionally can comprise erosion and biodegradation enhancers which facilitate the erosion of the matrix, the dissolution of the core composition, or the uptake of the core composition via metabolic processes. Particularly suitable erosion and biodegradation enhancers are biodegradable in biological fluids, and biocompatible. Hydrophilic constituents are typical, because they are capable of enhancing the erosion of the implant in the presence of biological fluids. For example, K. Juni *et al.*, Chem. Pharm. Bull., 33, 1609 (1985) disclose that the release rate of bleomycin from polylactic acid microspheres is greatly enhanced by incorporating fatty acid esters into the microspheres. Other exemplary hydrophilic constituents are described, for example, in Wade & Weller, Handbook of pharmaceutical Excipients (London: Pharmaceutical Press; Washington D.C.: American Pharmaceutical Ass'n 1995), and include the polyethylene glycols ("PEGs"), propylene glycol ("PG"), glycerin, and sorbitol.

Surfactants further enhance the erosion of the matrix and the release of the drug. Surfactants are generally capable of increasing the wettability and the solubility of the base composition in biological fluids, and thereby causing the disintegration and erosion of the implant. Surfactants can also help to break down the core composition matrix when, for example, the method of forming the dosage form has reduced the solubility of any of the constituents. Surfactants can also improve the uptake of the dosage forms into the

What is claimed is:

1) A method of treating a hyperproliferative disorder comprising administering an antiproliferative agent in combination with a potentiating effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof.

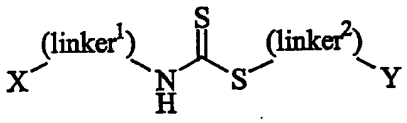
2) The method of claim 1 wherein the hyperproliferative disorder is a tumor.

3) The method of claim 1 wherein the hyperproliferative disorder is a tumor, and the antiproliferative agent is a chemotherapeutic agent.

4) The method of claim 3 wherein the chemotherapeutic agent is 5-fluorouracil.

5) The method of claim 3 wherein the chemotherapeutic agent is FdUMP, cisplatin, etoposide, adriamycin, or 5-aza-2'-deoxycytidine.

6) The method of claim 3 wherein the *N*-substituted dithiocarbamate is defined by the following formula (I):



(I)

wherein:

a) X is selected from alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted;

b) Y is selected independently from H, CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, C(O)(OR), amino acid, alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted; and wherein R, R^1 and R^2 are independently H, alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl which can be optionally substituted;

c) linker ^{1} and linker ^{2} are independently alkyl, alkenyl, alkynyl, heterocyclic, heteroaryl, aryl, aralkyl, heterocyclicalkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl, which can be optionally substituted and wherein linker^1 can be a direct bond.

heteroaryl, aryl, aralkyl, heterocycle-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 1-3; and

f) m is 1-12.

11) The method of claim 10 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic ring;

b) Y is COOR;

c) n is 1-3; and

d) m is 1-10, preferably 1-5.

12) The method of claim 10 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is $C(O)NR^1R^2$;

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 1-3; and

e) m is 1-10.

13) The method of claim 10 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

14) The method of claim 10 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)R;

c) R is lower alkyl, preferably methyl;

d) n is 1-3; and

e) m is 1-10.

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

19) The method of claim 17 wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is $COOCH_3$;

c) n is 0-3; and

d) m is 1-10, preferably 1-5.

20) The method of claim 17 wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

21) The method of claim 17 wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

22) The method of claim 17 wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

23) The method of claim 17 wherein:

a) X is substituted or unsubstituted aryl or heteroaryl;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

d) n is 1-3; and

e) m is 1-10.

27) The method of claim 24 wherein:

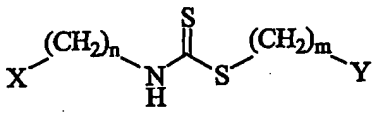
a) X is a substituted or unsubstituted 2- or 3- benzofuran, benzothiophene, or indole;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 1-3; and

d) m is 1-5.

28) The method of claim 3 wherein the dithiocarbamate is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted alkyl group;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

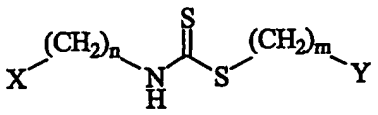
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

29) The method of claim 3 wherein the dithiocarbamate is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic,

32) The method of claim 30 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is an amino acid;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

33) The method of claim 30 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

34) The method of claim 30 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is C(O)R;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

35) The method of claim 30 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid benzyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,4- dichloro-benzyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid phenyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 4-chloro- phenyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,4- difluoro-phenyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-3- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-3-ylmethyl ester;

4-((S)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

4-((R)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

3-(Furan-2-ylmethylthiocarbamoyl- sulfanyl)propionic acid methyl ester;

3-(Methylthiocarbamoylsulfanyl)propionic acid methyl ester;

3-(Ethoxycarbonylthiocarbamoylsulfanyl) propionic acid methyl ester;

4-(2-Methoxy-ethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrofuran-2-ylmethylsulfanyllthio- carbonylamino)butyric acid ethyl ester;

4-(Cyclohexylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzylthiocarbamoylsulfanyl)butyric acid methyl ester;

Methyldithiocarbamic acid methyl ester;

4-(1-Methylpyrrolidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1*H*-Pyrrol-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1*H*-Pyrrol-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(5-Oxo-pyrrolidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1-Methyl-5-oxo-pyrrolidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyridin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1-Methylpiperidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrazin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrimidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

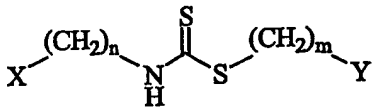
4-(Thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrothiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzo[*b*]thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester; and

4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester.

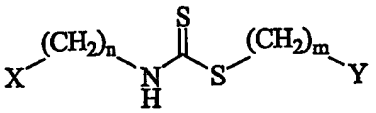
39) A method of treating a disorder of hyperproliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein X is a heterocycle or heteroaromatic moiety; Y is CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, or C(O)(OR); n is 1, 2, 3, or 4 and m is 1, 2, 3, 4, 5, or 6.

40) A method of treating a disorder of hyperproliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

43) The method of claim 41 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is $C(O)NR^1R^2$;

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 1-3; and

e) m is 1-10.

44) The method of claim 41 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

45) The method of claim 41 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)R;

c) R is lower alkyl, preferably methyl;

d) n is 1-3; and

e) m is 1-10.

46) The method of claim 41 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is an optionally substituted aryl, heteroaryl, or heterocyclic;

c) n is 1-3; and

d) m is 1-5.

47) The method of claim 41 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 1-3; and

f) m is 1-5.

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

52) The method of claim 48 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

53) The method of claim 48 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

54) The method of claim 48 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

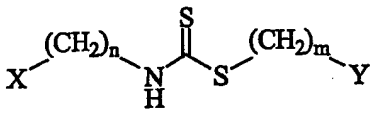
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-5.

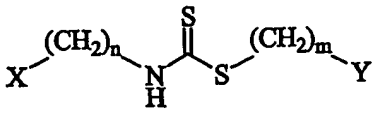
55) A method of treating a disorder of proliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted alkyl group;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

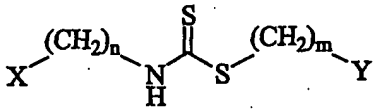
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

60) A method of treating a disorder of proliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

d) n is 1-3; and

e) m is 1-10.

64) The method of claim 61 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

65) The method of claim 61 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is C(O)R;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

66) The method of claim 61 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

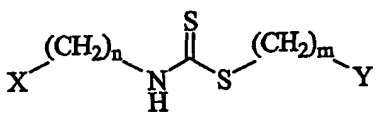
b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

67) A method of treating a disorder of proliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-3-ylmethyl ester;

4-((S)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

4-((R)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

3-(Furan-2-ylmethylthiocarbamoyl- sulfanyl)propionic acid methyl ester;

3-(Methylthiocarbamoylsulfanyl)propionic acid methyl ester;

3-(Ethoxycarbonylthiocarbamoylsulfanyl) propionic acid methyl ester;

4-(2-Methoxy-ethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrofuran-2-ylmethylsulfanyllthio- carbonylamino)butyric acid ethyl ester;

4-(Cyclohexylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzylthiocarbamoylsulfanyl)butyric acid methyl ester;

Methyldithiocarbamic acid methyl ester;

(5-Chloro-2-methyl-phenyl)dithiocarbamic acid ethyl ester;

4-[2-(1*H*-Indol-2-yl)ethylthiocarbamoyl-sulfanyl]butyric acid methyl ester;

(2-Amino-3-benzylthiocarbamoylsulfanyl)propionic acid;

(3-Methoxybenzyl)dithiocarbamic acid 3,3-dimethyl-2-oxo-butyl ester;

(Pyridin-3-ylmethyl)dithiocarbamic acid 2,5-dichloro-thiophen-3-ylmethyl ester;

4-(1-Methyl-5-oxo-pyrrolidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyridin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1-Methylpiperidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrazin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrimidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

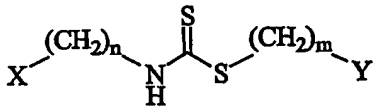
4-(Thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrothiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzo[*b*]thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester; and

4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester.

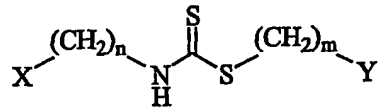
70) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein X is a heterocycle or heteroaromatic moiety; Y is CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, or C(O)(OR); n is 1, 2, 3, or 4 and m is 1, 2, 3, 4, 5, or 6.

71) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein

a) X is tetrahydrofuran;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic,

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 1-3; and

e) m is 1-10.

75) The method of claim 72 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

76) The method of claim 72 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)R;

c) R is lower alkyl, preferably methyl;

d) n is 1-3; and

e) m is 1-10.

77) The method of claim 72 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is an optionally substituted aryl, heteroaryl, or heterocyclic;

c) n is 1-3; and

d) m is 1-5.

78) The method of claim 72 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 1-3; and

f) m is 1-5.

79) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

83) The method of claim 79 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

84) The method of claim 79 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

85) The method of claim 79 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

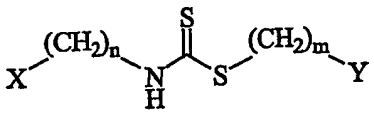
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-5.

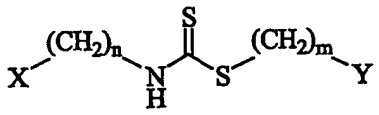
86) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted alkyl group;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

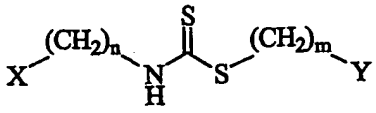
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

91) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

d) n is 1-3; and

e) m is 1-10.

95) The method of claim 92 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

96) The method of claim 92 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is C(O)R;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

97) The method of claim 92 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

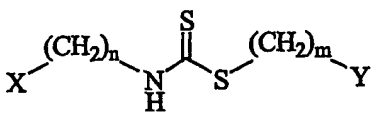
b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

98) A method of treating a VCAM-1 mediated condition comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-3- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-3-ylmethyl ester;

4-((S)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

4-((R)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

3-(Furan-2-ylmethylthiocarbamoyl- sulfanyl)propionic acid methyl ester;

3-(Methylthiocarbamoylsulfanyl)propionic acid methyl ester;

3-(Ethoxycarbonylthiocarbamoylsulfanyl) propionic acid methyl ester;

4-(2-Methoxy-ethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrofuran-2-ylmethylsulfanyllthio- carbonylamino)butyric acid ethyl ester;

4-(Cyclohexylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzylthiocarbamoylsulfanyl)butyric acid methyl ester;

Methyldithiocarbamic acid methyl ester;

(5-Chloro-2-methyl-phenyl)dithiocarbamic acid ethyl ester;

4-[2-(1*H*-Indol-2-yl)ethylthiocarbamoyl- sulfanyl]butyric acid methyl ester;

(2-Amino-3-benzylthiocarbamoylsulfanyl)propionic acid;

(3-Methoxybenzyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Pyridin-3-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

4-(1-Methyl-5-oxo-pyrrolidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyridin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(1-Methylpiperidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrazin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrimidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

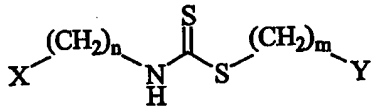
4-(Thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrothiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzo[*b*]thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester; and

4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester.

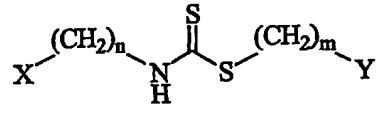
101) A method of treating a disorder of proliferation comprising administering an effective amount of a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein X is a heterocycle or heteroaromatic moiety; Y is CN, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, or C(O)(OR); n is 1, 2, 3, or 4 and m is 1, 2, 3, 4, 5, or 6.

102) A pharmaceutical composition comprising a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein

a) X is tetrahydrofuran;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic,

d) n is 1-3; and

e) m is 1-10.

106) The pharmaceutical composition of claim 103 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)OR;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10, preferably 1-5.

107) The pharmaceutical composition of claim 103 wherein:

a) X is a substituted or unsubstituted 5 or 6 membered heterocyclic;

b) Y is C(O)R;

c) R is lower alkyl, preferably methyl;

d) n is 1-3; and

e) m is 1-10.

108) The pharmaceutical composition of claim 103 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is an optionally substituted aryl, heteroaryl, or heterocyclic;

c) n is 1-3; and

d) m is 1-5.

109) The pharmaceutical composition of claim 103 wherein:

a) X is an optionally substituted 5 or 6 membered heterocyclic;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 1-3; and

f) m is 1-5.

c) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

d) n is 0-3; and

e) m is 1-10, preferably 1-5.

114) The pharmaceutical composition of claim 110 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is C(O)R;

c) R is lower alkyl;

d) n is 0-3; and

e) m is 1-10.

115) The pharmaceutical composition of claim 110 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) n is 0-3; and

d) m is 1-5.

116) The pharmaceutical composition of claim 110 wherein:

a) X is substituted or unsubstituted heteroaryl;

b) Y is CN, H, NR^1R^2, or $CH(NR^1R^2)C(O)OR$;

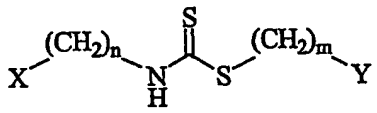
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H, substituted or unsubstituted alkyl, or together with N constitute a 3, 4, 5, 6, or 7 membered heterocyclic or heteroaromatic bridge, such as $-(CH_2)_m-$ wherein m is 2, 3, 4, 5, or 6;

e) n is 0-3; and

f) m is 1-5.

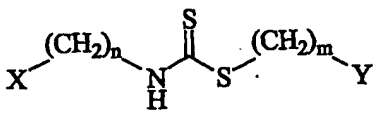
117) A pharmaceutical composition comprising a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

121) A pharmaceutical composition comprising a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted alkyl group;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

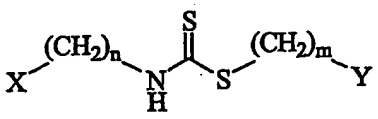
c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

122) A pharmaceutical composition comprising a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

a) X is a substituted or unsubstituted carbohydrate;

b) Y is H, CN or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, OR, OC(O)R, $C(O)NR^1R^2$, C(O)R, NR^1R^2, heterocyclic, heteroaryl, aryl, aralkyl, heterocycyclic-alkyl, heteroarylalkyl, alkaryl, alkylheterocyclic, or alkylheteroaryl;

c) R is H or substituted or unsubstituted lower alkyl;

d) R^1 and R^2 are independently H or substituted or unsubstituted lower alkyl;

e) n is 1-3; and

f) m is 1-12.

e) m is 1-10.

126) The pharmaceutical composition of claim 123 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is $C(O)NR^1R^2$;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

127) The pharmaceutical composition of claim 123 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

b) Y is C(O)R;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

128) The pharmaceutical composition of claim 123 wherein:

a) X is substituted or unsubstituted heterocyclic, heteroaryl, heteroarylalkyl or heterocyclicalkyl, wherein the heterocyclic or heteroaryl binds to the molecule through a carbon in the ring of the heterocyclic or heteroaryl;

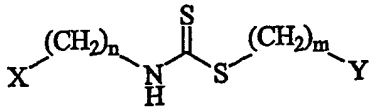
b) Y is substituted or unsubstituted aryl, heteroaryl, or heterocyclic;

c) R is H or lower alkyl;

d) n is 1-3; and

e) m is 1-10.

129) A pharmaceutical composition comprising a *N*-substituted dithiocarbamate ester, or a pharmaceutically acceptable salt thereof, wherein the *N*-substituted dithiocarbamate ester is defined by the following structure (II):



(II)

wherein:

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrothiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid thiophen- 3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-2-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid tetrahydrofuran-3-ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid furan-3- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-2- ylmethyl ester;

(Tetrahydrofuran-2-ylmethyl)dithiocarbamic acid pyridin-3-ylmethyl ester;

4-((S)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

4-((R)-Tetrahydrofuran-2-ylmethylthiocarbamoyl- sulfanyl)butyric acid methyl ester;

3-(Furan-2-ylmethylthiocarbamoyl- sulfanyl)propionic acid methyl ester;

3-(Methylthiocarbamoylsulfanyl)propionic acid methyl ester;

3-(Ethoxycarbonylthiocarbamoylsulfanyl) propionic acid methyl ester;

4-(2-Methoxy-ethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrofuran-2-ylmethylsulfanyllthio- carbonylamino)butyric acid ethyl ester;

4-(Cyclohexylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzylthiocarbamoylsulfanyl)butyric acid methyl ester;

Methyldithiocarbamic acid methyl ester;

(5-Chloro-2-methyl-phenyl)dithiocarbamic acid ethyl ester;

4-[2-(1*H*-Indol-2-yl)ethylthiocarbamoyl- sulfanyl]butyric acid methyl ester;

(2-Amino-3-benzylthiocarbamoylsulfanyl)propionic acid;

(3-Methoxybenzyl)dithiocarbamic acid 3,3- dimethyl-2-oxo-butyl ester;

(Pyridin-3-ylmethyl)dithiocarbamic acid 2,5- dichloro-thiophen-3-ylmethyl ester;

Allyldithiocarbamic acid 2-aminoethyl ester hydrochloride;

(2,4-dichlorobenzyl)dithiocarbamic acid 2,4- dichlorobenzyl ester;

Phenethyldithiocarbamic acid dodecyl ester;

4-(Pyrazin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Pyrimidin-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Tetrahydrothiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester;

4-(Benzo[*b*]thiophen-2-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester; and

4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester,

or a pharmaceutically acceptable salt thereof.

131) The method of claim 70 wherein the VCAM mediated disease is a noncardiovascular inflammatory disease selected from rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and chronic solid organ rejection, and multiple sclerosis.

132) The method of claim 70 wherein the VCAM-mediated disease is a cardiovascular disease selected from atherosclerosis, post-angioplasty restenosis, coronary artery disease, angina and small artery disease.

133) The method of claim 71 wherein the VCAM mediated disease is a noncardiovascular inflammatory disease selected from rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and chronic solid organ rejection, and multiple sclerosis.

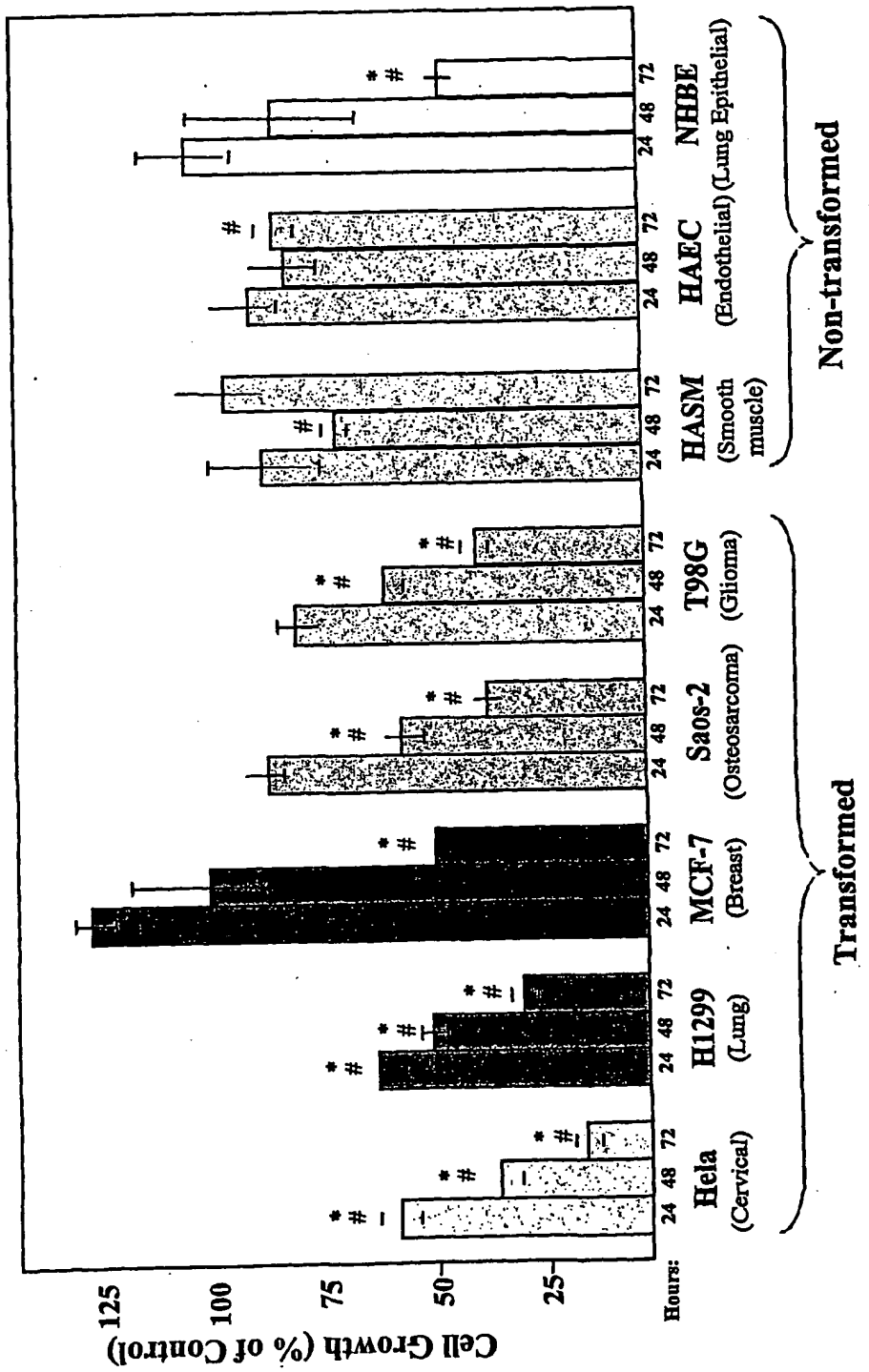
134) The method of claim 71 wherein the VCAM-mediated disease is a cardiovascular disease selected from atherosclerosis, post-angioplasty restenosis, coronary artery disease, angina and small artery disease.

135) The method of claim 72 wherein the VCAM mediated disease is a noncardiovascular inflammatory disease selected from rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and chronic solid organ rejection, and multiple sclerosis.

136) The method of claim 72 wherein the VCAM-mediated disease is a cardiovascular disease selected from atherosclerosis, post-angioplasty restenosis, coronary artery disease, angina and small artery disease.

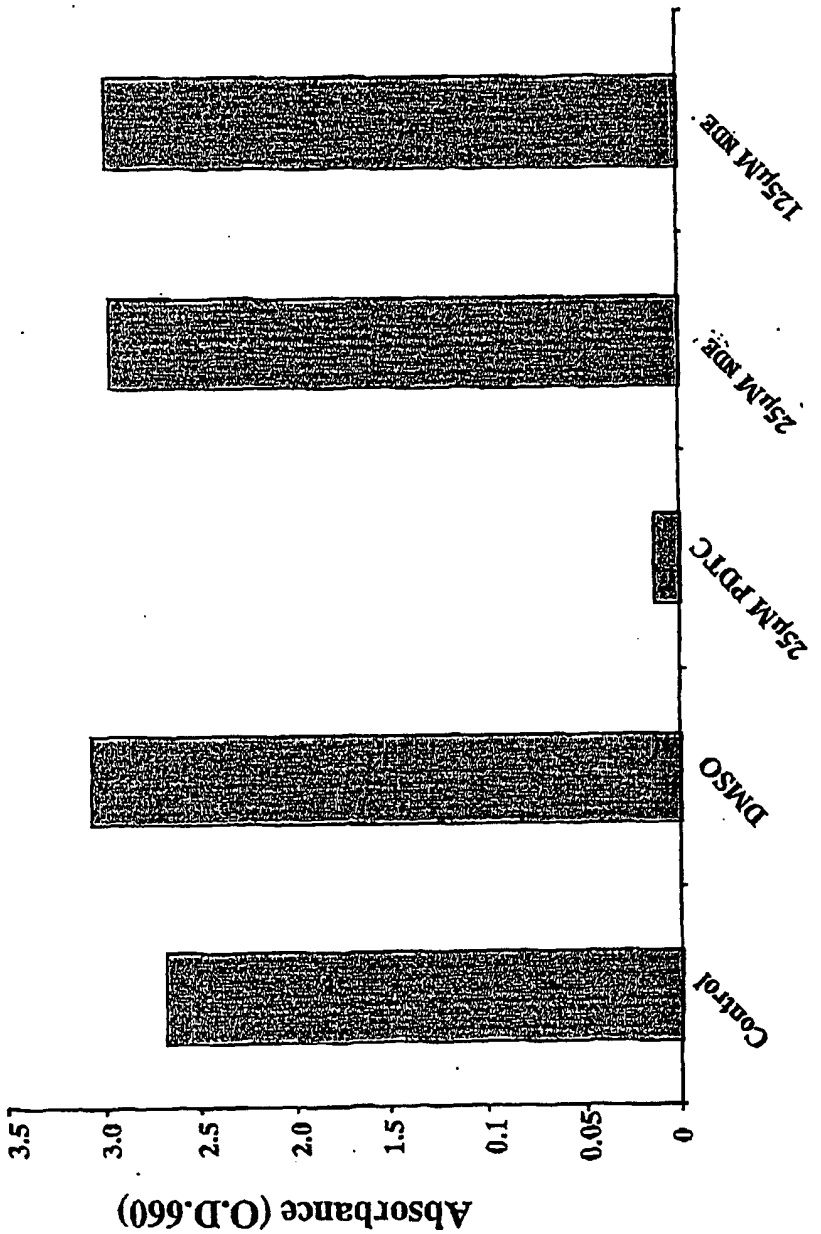
137) The method of claim 78 wherein the VCAM mediated disease is a noncardiovascular inflammatory disease selected from rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and chronic solid organ rejection, and multiple sclerosis.

Figure 1



4-(Benzo[*b*]thiophen-3-ylmethylthiocarbamoylsulfanyl)butyric acid methyl ester.

Figure 3: NDE is not an antioxidant as determined by the LMB assay



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